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CLAIMS:

1. A combination of substances, at least two of which exhibit amphipatic properties when contacted with a suitable liquid medium, said two substances differing in their solubility in this medium and said combination being capable of forming extended surfaces, especially membrane surfaces, in contact with said medium, such that molecules of an amphipatic third substance can associate with said surface, wherein said at least two substances are selected so that
- substance which is more soluble in said liquid medium than the other substance forms less extended surfaces than said other substance of the combination and
 - molecules of the third substance are more likely to associate with the extended surfaces formed by the other at least two substances combined than with an extended surface formed by said other, less soluble substance alone.
2. A combination of substances, at least two of which exhibit amphipatic properties when contacted with a suitable liquid medium, said two substances being capable of forming, at least when combined, an extended surface, especially a membrane surface, in contact with said medium, said surface carrying a net electric charge, such that molecules of a further amphipatic substance with a net electric charge can associate with said surface, and the net charge density of the surface and the net charge of the amphipatic molecules associating with the surface have the same sign (both negative or both positive).
3. A combination of substances, at least two of which exhibit amphipatic properties when contacted with a suitable liquid medium said two substances differing in their solubility in this medium and being capable of forming, at least when combined, extended surfaces, especially membrane surfaces, in contact with said medium, such that molecules of an amphipatic third substance can associate with said surfaces, said at least two substances being selected so that
- the substance which is more soluble in said liquid medium than the other substance forms less extended surfaces than said other substance of the combination,

5 -the surfaces formed by the combined substances as well as the molecules of the third substance likely to associate with said surface, are both negatively charged or both positively charged.

4. A combination according to claim 1, ~~2 or 3~~,
characterised in that it comprises at least one amphipatic substance capable of self-aggregating to form an extended surface, which becomes more flexible when said substance is mixed with other combination components, especially with an amphipatic substance which is more soluble in the liquid medium than said self-aggregating substance, and especially where said two substances differ in solubility in the medium at least 10-fold, and preferably at least 100-fold.

5. A combination according to ~~claims 1, 2 or 3;~~
characterised in that it comprises at least one amphipathic substance capable of self-aggregating to form an extended surface, and at least one amphipathic substance which, when incorporated into said surface, supports an increased curvature of said surface, the concentration of said curvature-increasing substance being below 99% of the saturation concentration, or of that concentration above which the surface could not be formed, whichever is higher.

6. A combination according to claim 4 ~~or 5~~,
characterised in that the concentration of said more soluble or curvature-increasing substance amounts to at least 0.1 %, frequently to 1-80 %, more preferably to 10-60 %, and most preferably to 20-50 % of the relative concentration as defined in claim 5.

7. A combination according to claim 5 ~~or 6~~,
characterised in that the surfaces have an average curvature (defined as the inverse
average radius of the areas enclosed by the surfaces) corresponding to an average radius

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5 **characterised in that** the surface is supported by a solid, especially by a supporting surface of suitable curvature or size

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characterised in that the substance which is less soluble in the liquid medium, and which preferably is the surface-building and/or charge carrying amphipatic substance in the system, is a lipid or lipid-like material, whereas the substance which is more soluble in the liquid medium, and preferably is the substance causing increased surface curvature, flexibility or adaptability and/or is the charge carrying substance, is a surfactant, or is identical with the third, associating substance.

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characterised in that it comprises arrangements of molecules in the form of minute fluid droplets suspended or dispersed in a liquid medium and surrounded by a membrane-like coating of one or several layers of at least two kinds or forms of self-aggregating amphiphilic substances, said at least two substances having an at least 10-fold, preferably an at least 100-fold difference in solubility in the preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or of hetero-aggregates of both substances is smaller than the average diameter of homo-aggregates of the less soluble substance.

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claim

14. Combination according to ~~any one of the preceding claims~~, wherein the total content of all amphipats that can form a surface is between 0.01 and 30 weight-%, particularly between 0.1 and 15 weight-%, and most preferably between 1 and 10 weight-% of the total dry mass of the aggregates, especially if the combination is to be applied on or in the human or animal body.

Claim

15. Combination according to ~~any one of the preceding claims,~~
characterised in that it contains at least one (bio)compatible polar or non-polar
 surface-supporting lipid as the substance which forms more extended surfaces, wherein
 20 the surfaces formed by the combination preferably have a bilayer structure.

16. Combination according to claim 15, wherein said extended surface-forming substance is a lipid or a lipoid from a biological source or a corresponding synthetic lipid, or is a modification of such a lipid, preferably a glyceride, glycerophospholipid; isoprenoidlipid, sphingolipid, steroid, sterine or sterol, a sulphur- or carbohydrate-containing lipid, or any other lipid capable of forming bilayers, in particular a half-protonated fluid fatty acid, and preferably selected from phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, phosphatidylserines, sphingomyelins or sphingophospholipids, glycosphingolipids (e.g. it is a cerebroside, ceramidpolyhexoside, sulphatide, sphingoplasmalogene), gangliosides, or other glycolipids or synthetic lipids, in particular of the dioleoyl-, dilinoleyl-, dilinolenyl-,

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- 5 17. Combination according to any of claims 12 through 16, wherein said
surfactant is a nonionic, a zwitterionic, an anionic or a cationic surfactant, especially a
long-chain fatty acid or alcohol, an alkyl-tri/di/methyl-ammonium salt, an alkylsulphate
salt, a monovalent salt of cholate, deoxycholate, glycocholate, glycodeoxycholate,
taurodeoxycholate, or taurocholate, an acyl- or alkanoyl-dimethyl-aminoxide, esp. a
10 dodecyl- dimethyl-aminoxide, an alkyl- or alkanoyl-N-methylglucamide, N-alkyl-N,N-
dimethylglycine, 3-(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a
polyethylen-glycol-octylphenyl ether, esp. a nonaethylen-glycol-octylphenyl ether, a
polyethylene-acyl ether, esp. a nonaethylen-dodecyl ether, a polyethyleneglycol-isoacyl
ether, esp. a octaethyleneglycol-isotridecyl ether, polyethylene-acyl ether, esp.
15 octaethylenedodecyl ether, polyethyleneglycol-sorbitane-acyl ester, such as
polyethylenglykol-20-monolaurate (Tween 20) or polyethylenglykol-20-sorbitan-
monooleate (Tween 80), a polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene-
lauryl, -myristoyl, -cetylstearyl, or -oleoyl ether, as in polyhydroxyethylen-4 or 6 or 8 or
10 or 12, etc. -lauryl ether (as in Brij series), or in the corresponding ester, e.g. of
20 polyhydroxyethylen-8-stearate (Myrj 45), -laurate or -oleate type, or in polyethoxylated
castor oil 40 (Cremophor EL), a sorbitane-monoalkylate (e.g. in Arlacel or Span), esp.
sorbitane-monolaurate (Arlacel 20, Span 20), an acyl- or alkanoyl-N-methylglucamide,
esp. in or decanoyl- or dodecanoyl-N-methylglucamide, an alkyl-sulphate (salt), e.g. in
lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium glycodeoxycholate, sodium
25 oleate, sodium taurate, a fatty acid salt, such as sodium elaidate, sodium linoleate,
sodium laurate, a lysophospholipid, such as n-octadecylene(=oleoyl)-
glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-acyl-, e.g. lauryl
or oleoyl-glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-
tetradecyl- glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, a
30 corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospholipid or a corresponding
short-chain phospholipid, or else a surface-active polypeptide.

64 Claim 12

characterised in that the surface formed from the combination contains charged membrane components in the relative concentration range 1 to 80 mol-%, preferably 10 to 60 mol-% and most preferred between 30 and 50 mol-%.

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characterised in that a phosphatidylcholine and/or a phosphatidylglycerol is the surface-supporting substance and a lysophospholipid, such as lysophosphatidic acid or methylphosphatidic acid, lysophosphatidylglycerol, or lysophosphatidylcholine, or a partially N-methylated lysophosphatidylethanolamine, a monovalent salt of cholate, deoxycholate-, glycocholate, glycodeoxycholate- or any other sufficiently polar sterol derivative, a laurate, myristate, palmitate, oleate, palmitoleate, elaidate or some other fatty acid salt and/or a Tween-, a Myrj- or a Brij-type, or else a Triton, a fatty-sulphonate or -sulphobetaine, -N-glucamide or -sorbitane (Arlacel or Span) surfactant is the substance less capable of forming the extended surface.

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characterised in that the average radius of the areas enclosed by said extended surfaces is between 15 nm and 5000 nm, often between 30 nm and 1000 nm, more often between 40 nm and 300 nm and most preferably between 50 nm and 150 nm.

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Claim 11

characterised in that the third substance, which can associate with the extended surface, comprises contains repeating subunits, especially in the form of chain molecules, such as oligomers or polymers, especially with an average molecular weight above 800 Daltons, preferably above 1000 Daltons and often even above 1500 Daltons.

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characterised in that the third substance is of biological origin, and preferably is bioactive.

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65 *Claim 1*
23. Combination according to ~~any one of claims 1 through 22,~~

characterised in that the third substance associates with the membrane-like extended surface, especially by inserting itself in the interface(s) between the membrane and the liquid medium in contact with said membrane.

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Claim 1
24. Combination according to ~~any one of claims 1 to 23,~~ wherein the content

of chain molecules corresponding to said third substance, is between 0.001 and 50 rel.

% compared to the mass of adsorbent surface and often is between 0.1 and 35 rel. %,

more preferably is between 0.5 and 25 rel. %, and most suitably is between 1 and 20

10 rel. %, whereby the specific ratio value is likely to decrease with increasing molar mass of said chain molecules.

Claim 21
25. Combination according to ~~any one of claims 21 through 24,~~ wherein

chain molecule is a protein, and at least a part of said molecule is associated with the

15 surface, provided that such part has at least three segments or functional groups with a propensity to bind to said surface.

Claim 21
26. Combination according to ~~any one of claims 21 through 24,~~

characterised in that said chain molecules belong to the class of polynucleotides, such

20 as DNA or RNA, in the natural form or after chemical, biochemical, or genetic modification.

Claim 21
27. Combination according to ~~any one of claims 21 through 24,~~

characterised in that said chain molecules belong to the class of polysaccharides with

25 at least partial propensity to interact with the surface either in the natural form or after some chemical, biochemical, or genetic modification.

Claim 21
28. Combination according to ~~any one of claims 21 through 27,~~ wherein the

chain molecule can act as an adrenocorticostaticum, a β -adrenolyticum, an androgen or

30 antiandrogen, antiparasiticum, anabolicum, anaestheticum or analgesicum, analepticum,

antiallergicum, antiarrhythmicum, antiarteroscleroticum, antiasthmaticum and/or

bronchospasmolyticum, antibioticum, antidrepressivum and/or antipsychoticum,

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20 29. Combination according to ~~any one of the preceding claims~~, wherein said
third substance chain molecule or agent is a growth modulating substance.

31. Combination according to ~~any one of the preceding claims~~, wherein said third substance agent is an enzyme, a co-enzyme or some other kind of bio-catalyst.

67 *Claim 1*

32. Combination according to ~~any one of the preceding claims~~, wherein said third substance agent is a recognition molecule, including inter alia adherins, antibodies, catenins, selectins, chaperones, or parts thereof.

Claim 1

5 33. Combination according to ~~any one of the preceding claims~~, wherein said agent is a hormone, especially insulin.

Claim 1

34. Combination according to ~~any one of the preceding claims~~,
characterised in that it contains 1 through to 500 I.U. insulin/mL, in particular
10 between 20 and 400 I.U. insulin/mL and most preferred between 50 and 250 I.U. insulin/mL, preferably of human recombinant or humanised type.

Claim 1

35. Combination according to ~~any one of the preceding claims~~,
characterised in that it contains between 0.01 mg and 20 mg interleukin/mL, in
15 particular between 0.1 and 15 mg and most preferred between 1 and 10 mg interleukin/mL, said interleukin being suitable for the use in humans or animals, including IL-2, IL-4, IL-8, IL-10, IL-12, if necessary after a final dilution to reach the practically desirable drug concentration range.

Claim 1

20 36. Combination according to ~~any one of the preceding claims~~,
characterised in that it contains up to 20 relative wt-% interferon, in particular between 0.1 and 15 mg interferon/mL and most preferred between 1 and 10 mg interferon/mL, said IF being suitable for the use in humans or animals, including but not
25 restricted to IF alpha, beta and gamma, can be used, if necessary after a final dilution that brings the drug concentration into practically preferred concentration range.

Claim 1

37. Combination according to ~~any one of the preceding claims~~,
characterised in that it contains up to 25 mg nerve growth factor (NGF) / mL suspension or up to 25 relative w-% of NGF as an agent, especially 0.1-15 rel. w-%
30 protein and most preferred between 1 and 10 rel. wt-% NGF, preferably human recombinant NGF and, if needed, diluted before use.

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characterised in that the suspension contains up to 25 mg of immunoglobulin(Ig)/mL suspension or up to 25 w-% of Ig relative to total lipid, preferably with 0.1 rel. w-% to 15 rel. w-% protein and most advisable with 1 rel. w-% to 10 rel w-% immunoglobulin, whereby the agent is used in the form of an intact antibody, part of it, or a biologically acceptable and active modification thereof.

10 characterised by the steps of

- selecting at least two amphipathic substances, which differ in their solubility in a suitable liquid medium, such substances being capable of forming an extended surface, especially a membrane surface, at least when combined in contact with said medium,
- such that an extended surface formed by the combination of substances is capable of attracting and associating with the active agent to a greater extent than the surface formed only from the substance which is less soluble in the liquid medium and forms more extended surfaces than the other substance alone.

20 **characterised in that** the combination of surface-forming substances is generated by filtration, pressure change or mechanical homogenisation, shaking, stirring, mixing, or by means of any other controlled mechanical fragmentation, in the presence of agent molecules.

in which the selected combination of surface forming substances is permitted to adsorb to, or in some other way is brought into permanent contact with, (a) suitable supporting solid surface(s), and then with the liquid medium by adding one substance after another or several at a time, whereby at least one of the later surface-forming steps is carried out in the presence of the agent that subsequently associates with the solid-supported surface.

claim 39

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25 46. The method of claim 45,
characterised in that at least one edge-active substance or a surfactant, at least one
amphiphilic substance, at least one hydrophilic fluid and the agent are separately mixed
and, if required, dissolved to form a solution, the resulting mixtures or solutions then
being combined to subsequently induce, preferably by action of mechanical energy, the
30 formation of the entities which associate with the agent molecules.

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~~any one of claims 45 through to 48~~

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claim 45

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claim 45

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claim 1
53. Use of a combination of substances in accordance with ~~any one of the~~
~~preceding claims~~, for the preparation of drug carriers, drug depots, or for any other kind
of medicinal or biological application.

5 54 Use of a combination of substances in accordance with ~~any one of the~~
~~preceding claims~~, in bioengineering or for genetic manipulations. *claim 1*

claim 1
55. Use of a combination of substances in accordance with ~~any one of the~~
~~preceding claims~~, in separation technology, for (bio)processing or for diagnostic
10 purposes.

claim 1
56. Use of a combination of substances in accordance with ~~any one of the~~
~~preceding claims~~ to stabilise surface-associating molecules, especially chain molecules,
that are at least partially amphipatic, such as (derivatised) proteins, polypeptides,
15 polynucleotides, or polysaccharides and/or in catalysing processes which involve such
molecules in the surface-associated state.

claim 1
57. Use of a combination of substances in accordance with ~~any one of the~~
~~preceding claims~~ to affect the kinetics and/or the reversibility of association or
20 dissociation between said surface-associating molecules and a complex, adaptable
surface, whereby the higher surface charge density and/or greater surface softness and/or
surface defect density speeds up the association, or the corresponding reduction slows
down the rate of association or else induces partial molecular dissociation.

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